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<b>(21) International Application Number:</b> PCT/US99/13887 <b>(22) International Filing Date:</b> 21 June 1999 (21.06.99)  <b>(30) Priority Data:</b> 60/090,527 24 June 1998 (24.06.98) US 9817167.1 6 August 1998 (06.08.98) GB  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> SCOLNICK, Edward, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> COMPOSITIONS AND METHODS FOR TREATING ELEVATED BLOOD CHOLESTEROL  <b>(57) Abstract</b>  The present invention relates to compositions and methods for treating elevated blood cholesterol in a mammal while counteracting the occurrence of potentially adverse side effects such as myopathy. The compositions useful herein comprise the combination of a pharmaceutically effective amount of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor ("HMG-CoA reductase inhibitor") and a geranylgeraniol compound to a mammal in need thereof.		

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TITLE OF THE INVENTION  
COMPOSITIONS AND METHODS FOR TREATING ELEVATED BLOOD  
CHOLESTEROL

5 CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority of U.S. provisional application  
Serial No. 60/090,527, filed June 24, 1998.

BRIEF DESCRIPTION OF THE INVENTION

10 The present invention relates to compositions and methods for treating  
elevated blood cholesterol in a mammal while counteracting potential adverse side  
effects such as myopathy. The compositions useful herein comprise the combination  
of a pharmaceutically effective amount of a 3-hydroxy-3-methylglutaryl coenzyme A  
15 reductase inhibitor (hereafter "HMG-CoA reductase inhibitor") and a geranylgeraniol  
compound to a mammal in need thereof.

BACKGROUND OF THE INVENTION

It has been clear for several decades that elevated blood cholesterol is a  
major risk factor for coronary heart disease, and many studies have shown that the risk  
20 of coronary heart disease (CHD) events can be reduced by lipid-lowering therapy.  
Prior to 1987, the lipid-lowering armamentarium was limited essentially to a low  
saturated fat and cholesterol diet, the bile acid sequestrants (cholestyramine and  
colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of  
these treatments have limited efficacy or tolerability, or both. Substantial reductions in  
25 LDL (low density lipoprotein) cholesterol accompanied by increases in HDL (high  
density lipoprotein) cholesterol could be achieved by the combination of a lipid-  
lowering diet and a bile acid sequestrant, with or without the addition of nicotinic acid.  
However, this therapy is not easy to administer or tolerate and was therefore often  
unsuccessful except in specialist lipid clinics. The fibrates produce a moderate  
30 reduction in LDL cholesterol accompanied by increased HDL cholesterol and a  
substantial reduction in triglycerides, and because they are well tolerated these drugs  
have been more widely used. Probucol produces only a small reduction in LDL  
cholesterol and also reduces HDL cholesterol, which, because of the strong inverse  
relationship between HDL cholesterol level and CHD risk, is generally considered  
35 undesirable. With the introduction of lovastatin, the first inhibitor of HMG-CoA

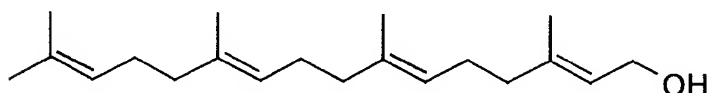
reductase to become available for prescription in 1987, for the first time physicians were able to obtain large reductions in plasma cholesterol with very few adverse effects.

Recent studies have unequivocally demonstrated that lovastatin, simvastatin and pravastatin, all members of the HMG-CoA reductase inhibitor class, slow the progression of atherosclerotic lesions in the coronary and carotid arteries. Simvastatin and pravastatin have also been shown to reduce the risk of coronary heart disease events, and in the case of simvastatin a highly significant reduction in the risk of coronary death and total mortality has been shown by the Scandinavian Simvastatin Survival Study. This study also provided some evidence for a reduction in cerebrovascular events.

However, along with their benefits, HMG-CoA reductase inhibitors can cause potentially adverse side effects such as myopathy and related disorders in a small percentage of patients. Myopathy is characterized by muscle pain and weakness. The Physician's Desk Reference, 42nd Ed., 1366 (1988), which is incorporated by reference herein in its entirety, states that myalgia, i.e. muscle pain, has been associated with lovastatin. Tobert, *N.E.J.Med.*, 48 (January 7, 1988), which is incorporated by reference herein in its entirety, states that in a very small number of patients (0.5 percent) myopathy appeared to be associated with lovastatin therapy. Concomitant therapy with immunosuppressant drugs, including cyclosporine, with gemfibrozil, or niacin, or a combination, appears to increase the risk of myopathy. See, J.A. Tobert, *Am.J. Cardiol.*, 1988, 62: 28J-34J, which is incorporated by reference herein in its entirety. The myopathy is reversible upon discontinuation of lovastatin therapy. See U.S. Patent 4, 933, 165, to Brown, issued June 12, 1990, which is incorporated by reference herein in its entirety. It is seen that it would be of considerable benefit to counteract the myopathy observed in the small percentage of patients. Therefore, improved therapies for treating, preventing, and reducing the risk of developing atherosclerosis, and cardiovascular and cerebrovascular events and related disorders are currently being sought which minimize the potential for adverse effects such as myopathy.

Geranylgeraniol and its derivatives belong to a class of naturally-occurring compounds known as terpenes. Terpenes are constructed of multiples of five-carbon isoprene units. See Lehninger, A.L., *Biochemistry*, 1975, pp. 296 and 682-683, which is incorporated by reference herein in its entirety.

For example, geranylgeraniol is a linear terpene containing four isoprene units, corresponding to the following chemical structure.



5

The geranylgeraniol derivative, geranylgeranyl pyrophosphate is an intermediate in the cholesterol biosynthetic pathway and is a substrate in the prenylation of proteins. See J.A. Glomset et al., *Geranylgeranylated proteins*, *Biochem-Soc-Trans.*, 1992 May, 20(2): 479-484, which is incorporated by reference  
10 herein in its entirety. Certain of these proteins, for example the small GTPases Rac, Rho, and Cdc42, regulate cytoskeletal function.

In cell cultures, geranylgeraniol is found to block apoptosis, i.e. programmed cell death that can be induced by an HMG-CoA reductase inhibitor. However, geranylgeraniol and its derivatives have not previously been investigated  
15 either *in vitro* or *in vivo* for their ability to mitigate the potentially adverse myopathy side effects that can be associated with HMG-CoA reductase inhibitor therapy for treating or preventing elevated blood cholesterol.

In the present invention, it is found that the combination of an HMG-CoA reductase inhibitor and a geranylgeraniol compound is effective for treating or  
20 preventing elevated blood cholesterol while mitigating the potentially adverse myopathy side effects that can be associated with the therapy. The combination has the advantage of providing increased safety and better patient compliance, which should maximize therapeutic efficacy. Without being limited by theory it is believed that the geranylgeraniol compound blocks the potentially harmful effect of the HMG-  
25 CoA reductase inhibitor on muscle cells. In other words, the geranylgeraniol compound is believed to interfere with apoptosis, or functional impair due to reduced geranylgeranylation, which can potentially be induced in muscle cells by the HMG-CoA reductase inhibitor.

It is an object of the present invention to provide compositions  
30 comprising the combination of an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

It is another object of the present invention to provide methods for treating or preventing elevated blood cholesterol in a mammal, particularly wherein said mammal is a human.

5 It is another object of the present invention to provide such methods while counteracting potential adverse myopathy effects.

It is another object of the present invention to provide such methods wherein the dosing is maintained until the desired therapeutic effect is achieved and/or maintained.

10 These and other objects will become readily apparent from the detailed description which follows.

#### SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

15 In further embodiments the present invention relates to a pharmaceutical composition comprising a pharmaceutically-effective amount of an HMG-CoA reductase inhibitor and an amount of a geranylgeraniol compound effective to counteract HMG-CoA reductase inhibitor-associated myopathy.

20 In further embodiments, the present invention relates to a method for treating or preventing elevated blood cholesterol in a mammal in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

25 In further embodiments, the present invention relates to a method for treating or preventing elevated blood cholesterol in a mammal in need thereof comprising sequentially administering a geranylgeraniol compound and an HMG-CoA reductase inhibitor.

30 In further embodiments, the present invention relates to the use of a composition in the manufacture of a medicament for treating or preventing elevated blood cholesterol in a mammal in need thereof, said composition comprising an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

In further embodiments, the present invention relates to the use of a composition comprising an HMG-CoA reductase inhibitor and a geranylgeraniol compound for treating or preventing elevated blood cholesterol in a mammal in need thereof.

All percentages and ratios used herein, unless otherwise indicated, are by weight. The invention hereof can comprise, consist of, or consist essentially of the essential as well as optional ingredients, components, and methods described herein.

## 5 BRIEF DESCRIPTION OF THE FIGURE

Figure 1 shows that activation of Mst1 cleavage by 10  $\mu$ M lovastatin is blocked by geranylgeraniol. Osteoclast-like cells are purified from cocultures by sequential treatment of culture dishes with collagenase and EDTA. Cells are then treated for 17 hours with lovastatin. Cell lysates are made and then analyzed by an in-  
10 gel kinase assay using myelin basic protein as a substrate. Lane 1 is a no-treatment control. Lane 2 shows treatment with 10  $\mu$ M lovastatin. Lane 3 shows treatment with the combination of 10  $\mu$ M Lovastatin and 10  $\mu$ M geranylgeraniol.

## DETAILED DESCRIPTION OF THE INVENTION

15 The present invention relates to compositions and methods for treating or preventing elevated blood cholesterol in a mammal in need of such treatment, while counteracting the occurrence of adverse myopathy effects. The compositions comprise a pharmaceutically effective amount of an HMG-CoA reductase inhibitor and a pharmaceutically effective amount of a geranylgeraniol compound.

20 The term "pharmaceutically effective amount", as used herein, means that amount of the HMG-CoA reductase inhibitor or geranylgeraniol compound that will elicit the desired therapeutic effect or response or provide the desired benefit when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the HMG-CoA reductase inhibitor is an amount  
25 that is effective for treating or preventing elevated blood cholesterol. A preferred pharmaceutically effective amount of the geranylgeraniol compound is an amount that will block or mitigate the occurrence of adverse myopathy effects, while not blocking, or only minimally blocking, the therapeutic blood cholesterol effects of the HMG-CoA reductase inhibitor.

30 The term "counteracting the occurrence of adverse myopathy effects", as used herein, means preventing, decreasing, or lessening the occurrence of unwanted side effects in the muscular effects, relative to treatment with a HMG-CoA reductase inhibitor alone.

35 The term "until the desired therapeutic effect is achieved and/or maintained", as used herein, means that the therapeutic agent or agents are

continuously administered, according to the dosing schedule chosen, up to the time that the clinical or medical effect sought for the disease or condition being treated is observed by the clinician or researcher. For methods of treatment of the present invention, the pharmaceutical composition is continuously administered until the  
5 desired change in blood cholesterol is observed. In such instances, achieving a decrease in blood cholesterol is a desired objective. For methods of prevention of the present invention, the pharmaceutical composition is continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of blood cholesterol level is often an objective as well as prevention of or reducing the  
10 risk of developing atherosclerotic disease or cardiovascular disorders such as heart attack and stroke.

#### Compositions of the present invention

The pharmaceutical compositions of the present invention comprise a  
15 pharmaceutically effective amount of an HMG-CoA reductase inhibitor and a pharmaceutically effective amount of a geranylgeraniol compound. These compositions are useful for treating or preventing elevated blood cholesterol in a mammal in need thereof while counteracting the potentially adverse effects, such as myopathy, that can be associated with the administration of the HMG-CoA reductase  
20 inhibitor.

#### HMG-CoA Reductase Inhibitor

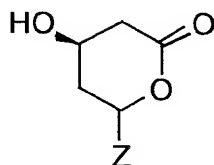
The compositions herein comprise a compound which inhibits the enzyme, HMG-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. *See*  
25 U.S. Patent No. 4,231,938, to Monaghan et al., issued November 4, 1980 and U.S. Patent No. 5,354,772, to Kathawal, issued October 11, 1994, both of which are incorporated by reference herein in their entirety.

Examples of HMG-CoA reductase inhibitors that are useful herein  
30 include but are not limited to lovastatin (MEVACOR®; see U.S. Patent No. 4,231,938, already cited above and incorporated by reference herein), simvastatin (ZOCOR®; see U.S. Patent No. 4,444,784, to Hoffman et al., issued April 24, 1984), pravastatin (PRAVACHOL®; see U.S. Patent No. 4,346,227, to Terahara et al., issued August 24, 1982), fluvastatin (LESCOL®; see U.S. Patent No. 5,354,772,  
35 already cited above and incorporated by reference herein), atorvastatin (LIPITOR®;



see U.S. Patent No. 5,273,995, to Roth, issued December 28, 1993) and cerivastatin (also known as rivastatin; see U.S. Patent No. 5,177,080, to Angerbauer et al., issued January 5, 1993); and mevastatin (compactin, see U.S. Patent No. 3,983,140, to Endo et al, issued September 28, 1976. The patents cited in the previous sentence not  
5 already incorporated by reference are also incorporated by reference herein in their entirety. The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the present invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 February 1996), which is incorporated by reference herein in its entirety. The term HMG-CoA  
10 reductase inhibitor is intended to include all pharmaceutically acceptable lactone and open acid (that is where the lactone ring is opened to form the free acid), as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such lactone, open acid, salt, and ester forms is included within the scope of this invention. Preferably, the HMG-CoA reductase  
15 inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, mevastatin, and the pharmaceutically acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof. More preferably, the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and the pharmaceutically  
20 acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof. More preferably, the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, and the pharmaceutically acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof.

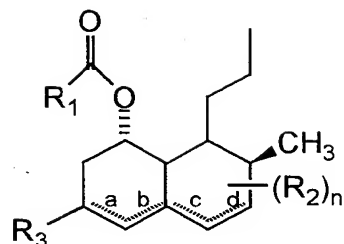
Preferred HMG-CoA reductase inhibitors can be represented by the  
25 chemical formula



(I)

wherein Z is selected from the group consisting of:

a)



wherein  $R^1$  is  $C_1$ - $C_{10}$  alkyl,

$R^2$  is selected from the group consisting of  $C_1$ - $C_3$  alkyl, hydroxy, oxo, and  $C_1$ - $C_3$

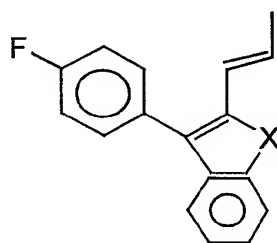
5 hydroxy substituted alkyl,

$R^3$  is selected from the group consisting of hydrogen, hydroxy,  $C_1$ - $C_3$  alkyl, and  $C_1$ - $C_3$  hydroxy substituted alkyl,

a, b, c, and d are all single bonds, or a and c are double bonds, or b and d are double bonds, or one of a, b, c, and d is a double bond, and

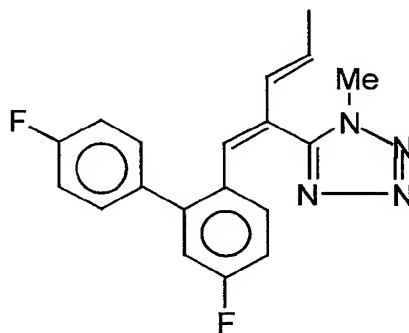
10 n is 0, 1, or 2;

b)

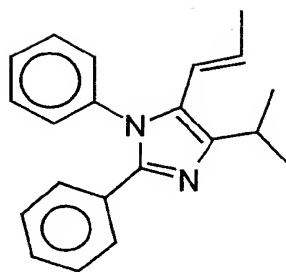


wherein X is selected from the group consisting of  $N[CH(CH_3)_2]$  and  $CH(CH_2)_3CH_3$

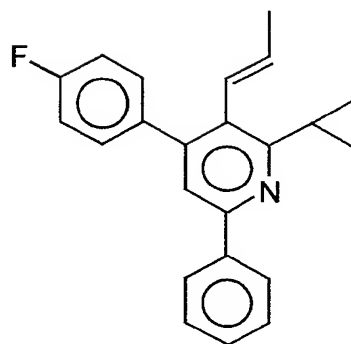
c)



d)



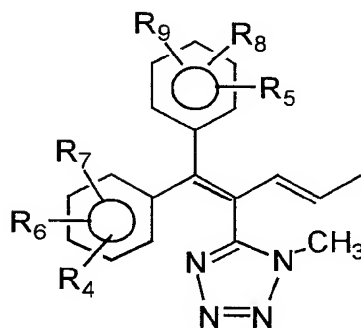
e)



and

5

f)



wherein R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of hydrogen, fluorine, chlorine, bromine, iodine, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and

trifluoromethyl, and R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, and R<sub>9</sub> are each independently selected from the group consisting of hydrogen, fluorine, chlorine, bromine, iodine, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy. *See* U.S. Patent No. 5,650,523, to DeCamp et al., issued July 22, 1997, which is incorporated by reference herein in its entirety. The pharmaceutically acceptable lactone, open acid, salt, and ester forms of the compounds depicted by the preceding chemical formulas are intended to be within the scope of the present invention.

The term "pharmaceutically acceptable salts" as used herein in referring to the HMG-CoA reductase inhibitors shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base. Examples of salt forms of HMG-CoA reductase inhibitors include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate, and mixtures thereof.

The term "esters" as used herein in referring to the HMG-CoA reductase inhibitors is used in its standard meaning to denote the condensation product of a carboxylic acid and an alcohol. Ester derivatives of the described compounds can function as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, can cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

The term "lactones" is used herein in referring to the HMG-CoA reductase inhibitors is used in its standard meaning to denote a cyclic condensation product of a carboxylic acid and an alcohol, i.e. a cyclic ester.

The term "open acid" is used herein in referring to the HMG-CoA reductase inhibitors to denote that the lactone ring is open, i.e. uncyclized, to form the free acid.

It is recognized that mixtures of two or more HMG-CoA reductase inhibitors can be utilized.

The dosage regimen utilizing a HMG-CoA reductase inhibitor is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amounts needed to prevent, counter, or arrest the progress of the condition. The term "patient" includes mammals, especially humans, who take an HMG-CoA reductase inhibitor or combination for any of the uses described herein. Administering of the drug or drugs to the patient includes both self-administration and administration to the patient by another person.

The precise dosage of the HMG-CoA reductase inhibitor will vary with the dosing schedule, the particular compound chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies.

In particular, for daily dosing, the amounts of the HMG-CoA reductase inhibitor can be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the Physicians' Desk Reference (PDR), 52<sup>nd</sup> Ed. of the PDR, 1998 (Medical Economics Co), which is incorporated by reference herein in its entirety. For the additional active agents, the doses can be the same or similar to those amounts which are known in the art.

The HMG-CoA reductase inhibitors can be administered via a wide variety of routes including oral administration, intravenous administration, intranasal administration, injections, ocular administration, and the like.

A preferred route of delivery is oral administration.

Oral dosage amounts of the HMG-CoA reductase inhibitor are from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA

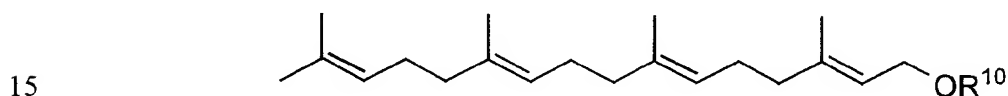
reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages. The HMG-CoA reductase inhibitor may be administered from 1 to 4 times per day, and preferably once per day.

For example, the daily dosage amount for simvastatin can be selected from 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg; for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; for pravastatin sodium, 10 mg, 20 mg, and 40 mg; and for atorvastatin calcium, 10 mg, 20 mg, and 40 mg.

### Geranylgeraniol Compounds

The compositions of the present invention comprise a pharmaceutically effective amount of a geranylgeraniol compound.

The geranylgeraniol compounds useful herein correspond to the chemical formula



wherein R<sup>10</sup> is selected from the group consisting of H (i.e. geranylgeraniol), C1-C30 alkyl (including straight, branched, and cyclic alkyl), C2-C30 alkenyl (including straight, branched, and cyclic alkenyl), C2-C30 alkynyl (including straight, branched, and cyclic alkynyl), C5-C14 aryl, PO<sub>3</sub>H<sub>2</sub> (i.e. geranylgeranyl phosphate), P<sub>2</sub>O<sub>7</sub>H<sub>3</sub> (i.e. geranylgeranyl pyrophosphate), C=O-R<sup>11</sup> (i.e. esters), wherein R<sup>11</sup> is selected from the group consisting of H, C1-C10 alkyl (including straight, branched, and cyclic alkyl), C2-C10 alkenyl (including straight, branched, and cyclic alkenyl), C2-C10 alkynyl (including straight, branched, and cyclic alkynyl), C2-C10 hydroxy-substituted alkyl (including straight, branched, and cyclic), C2-C10 amino-substituted alkyl (including straight, branched, and cyclic), C2-C10 carbonylhydroxy-substituted alkyl (including straight, branched, and cyclic), and C5-C14 aryl, and n is an integer from 0 to 3.

Preferably R<sup>10</sup> is selected from the group consisting of H, PO<sub>3</sub>H<sub>2</sub>, P<sub>2</sub>O<sub>7</sub>H<sub>3</sub>, and C=O-R<sup>11</sup>, wherein R<sup>11</sup> is selected from the group consisting of H, C1-C10 alkyl, C2-C10 hydroxy-substituted alkyl, C2-C10 amino-substituted alkyl, C2-C10 carbonylhydroxy-substituted alkyl, and C5-C14 aryl, and n is an integer from 2 to 3.

More preferably  $R^{10}$  is selected from the group consisting of H,  $PO_3H_2$ ,  $P_2O_7H_3$ , and  $C=O-R^{11}$ , wherein  $R^{11}$  is selected from the group consisting of H, C1-C10 alkyl, C2-C10 hydroxy-substituted alkyl, C2-C10 amino-substituted alkyl, C2-C10 carbonylhydroxy-substituted alkyl, and C5-C14 aryl, and n is 3.

5           The term "aryl," as used herein, refers to a monocyclic or polycyclic system comprising at least one aromatic ring, wherein the monocyclic or polycyclic system contains 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, or S, and wherein the monocyclic or polycyclic system is either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C1-10 alkyl, C3-8  
10   cycloalkyl, aryl, aryl C1-8 alkyl, amino, amino C1-8 alkyl, C1-3 acylamino, C1-3 acylamino C1-8 alkyl, C1-6 alkylamino, C1-6 alkylamino C1-8 alkyl, C1-6 dialkylamino, C1-6 dialkylamino-C1-8 alkyl, C1-4 alkoxy, C1-4 alkoxy C1-6 alkyl, hydroxycarbonyl, hydroxycarbonyl C1-6 alkyl, C1-5 alkoxycarbonyl, C1-3  
15   alkoxycarbonyl C1-6 alkyl, hydroxycarbonyl C1-6 alkyloxy, hydroxy, hydroxy C1-6 alkyl, cyano, trifluoromethyl, oxo or C1-5 alkylcarbonyloxy. Examples of aryl include, but are not limited to, phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, benzimidazolyl, indolyl, thienyl, furyl, dihydrobenzofuryl, benzo(1,3) dioxolane, oxazolyl, isoxazolyl and thiazolyl.

20           The esters are also intended to encompass esters of substituted acids such as lactic acid, amino acids, and other complex acids, and mono and higher esters of di and higher carboxylic acids such as succinic acid and glutaric acid.

Preferred geranylgeraniol compounds are selected from the group consisting of geranylgeraniol, geranylgeranyl ethyl ether, geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate,  
25   geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, geranylgeranyl glutarate, and mixtures thereof.

More preferred are geranylgeraniol, geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate,  
30   geranylgeranyl glutarate, and mixtures thereof.

Even more preferred herein are geranylgeraniol, geranylgeranyl pyrophosphate, and mixtures thereof.

It is recognized that mixtures of two or more of the geranylgeraniol compounds can be utilized.

The precise dosage of the geranylgeraniol compounds will also vary with the dosing schedule, the particular compound chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise  
5 pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount is chosen to counteract the potential adverse myopathy effects of the HMG-CoA reductase inhibitor. The amount should be below that level which will  
10 inhibit the desired cholesterol lowering effect of the HMG-CoA reductase inhibitor. For humans, an effective oral dose of the geranylgeraniol compound is typically chosen so as to provide a concentration in the blood stream from about 1  $\mu$ M to about 100  $\mu$ M, preferably about 10  $\mu$ M, although other ranges can be used. Nonlimiting exemplary doses are about 1 ug/kg to about 100 ug/kg, preferably about 10 ug/kg, for  
15 a human subject.

For the geranylgeraniol compound, human doses which can be administered are generally in the range of about 0.1 mg/day to about 10 mg/day, preferably from about 0.25 mg/day to about 5 mg/day, and more preferably from about 0.5 mg/day to about 1.5 mg/day, based on a geranylgeraniol active weight basis. A  
20 typical nonlimiting dosage amount would be about 0.75 mg/day. The pharmaceutical compositions herein comprise from about 0.1 mg to about 10 mg, preferably from about 0.25 mg to about 5 mg, and more preferably from about 0.5 mg to about 1.5 mg of the geranylgeraniol compound. A typical nonlimiting amount for is about 0.75 mg.

#### 25 Other components of the pharmaceutical compositions

The HMG-CoA reductase inhibitor and the geranylgeraniol compound are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers, collectively referred to herein as "carrier materials", suitably selected with respect to oral administration, i.e. tablets, capsules, elixirs, syrups,  
30 powders, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of a tablet, capsule, or powder, the active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid  
35 form, e.g., elixirs and syrups, the oral drug components can be combined with any



oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow  
5 lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The compounds used in the present method can also be coupled  
10 with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropyl-methacrylamide, and the like.

#### Methods of the Present Invention

15 The present invention comprises methods for treating or preventing elevated blood cholesterol in mammals. In preferred embodiments of the present invention, the mammal is a human.

The compositions and methods of the present invention are administered and carried out until the desired therapeutic effect is achieved.

20 In the methods of the present invention the HMG-CoA reductase inhibitor and the geranylgeraniol compound are generally administered concurrently. In alternate embodiments, the HMG-CoA reductase inhibitor and the geranylgeraniol compound can be administered sequentially. Preferably, the geranylgeraniol compound is administered first.

25 The following Examples are presented to better illustrate the invention.

#### EXAMPLE 1

##### Method for Evaluating the Effect of a HMG-CoA Reductase Inhibitor and a Geranylgeraniol Compound on Kinase Activities in Cultured Osteoclasts

30 Murine co-cultures of osteoblasts and marrow cells are prepared using the methods of Wesolowski, et al., *Exp Cell Res*, (1995), 219, pp. 679-686, which is incorporated by reference herein in its entirety. Bone marrow cells are harvested from 6-week-old male Balb/C mice by flushing marrow spaces of freshly isolated long bones (tibiae and femora) with  $\alpha$ -MEM (minimal essential media) containing

penicillin/streptomycin (100 I.U./ml of each and 20 mM Hepes buffer). The bone marrow cells are suspended in  $\alpha$ -MEM and the cells are filtered through an approximately 70  $\mu$ m cell strainer. The filtrate is centrifuged at about 300 x g for about 7 minutes. The resulting pellet is resuspended in  $\alpha$ -MEM supplemented with fetal calf serum (10 % v/v) and 10 nM 1, 25-(OH)<sub>2</sub> vitamin D<sub>3</sub>. These bone marrow isolates are added to sub-confluent monolayers of osteoblastic MB 1.8 cells in cell culture plates and cultured for 7 days at 37°C in the presence of 5% CO<sub>2</sub>. Culture media is replenished ever other day. Fusion of the osteoclast precursor cells from bone marrow (with each other) to form multinucleated osteoclast-like cells typically occurs after about 7 days. Osteoclast-like cells are enriched by sequential treatment with collagenase (1 mg/mL in phosphate buffered saline) for one hour at 37°C and EDTA (0.2 g/L in phosphate buffered saline) for 20 min at 37°C. Non-adherent cells are rinsed away by washing with phosphate buffered saline. Osteoclast-like cells which are resistant to the sequential treatments are present at about 95% purity and are maintained in  $\alpha$ -MEM supplemented with fetal calf serum (10 % v/v), 10 nM 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub>, macrophage-colony-stimulating factor (5 ng/mL).

The compounds to be evaluated are prepared as a solution of the desired concentration in  $\alpha$ -MEM. Examples of compounds that can be evaluated include HMG-CoA reductase inhibitors such lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, mevastatin, and the pharmaceutically acceptable salts, esters, and lactones thereof, as well as compounds that block the effects of these HMG-CoA reductase inhibitors, such as geranylgeraniol compounds, for example, geranylgeraniol, geranylgeranyl ethyl ether, geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, geranylgeranyl glutarate. Combinations of compounds can also be evaluated. The solutions of the compounds to be evaluated are added to the cultures for a time period of 17-24 hours. No treatment controls (controls not treated with compounds) are prepared by adding equivalent volumes of  $\alpha$ -MEM to the control dishes.

Cells are then harvested and lysed in a HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethansulfonic acid) or Tris buffer containing the following:  $\beta$ -glycerophosphate (50 mM); Na<sub>3</sub>VO<sub>4</sub> (1mM); NaF (1mM); Microcystin LR (1  $\mu$ M); leupeptin (10  $\mu$ g/ml); aprotinin (10  $\mu$ g/ml); phenylmethyl sulfonylfluoride (1 mM). Protein concentrations are determined for each lysate and 5-20  $\mu$ g are loaded into each lane of a SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel

electrophoresis) gel containing Myelin Basic Protein, or another kinase substrate, which has been polymerized into the gel at a concentration between 50-400 µg/ml. Molecular weight standards are also loaded into one or more lanes of the gels. In-gel kinase assays are run according to a standard procedure based on Kameshita and Fujisawa, 1989 (Anal. Biochem. 183:139-143) and of Gotoh et al., 1990 (Eur. J. Biochem. 193: 661-669), both references being incorporated by reference herein in their entirety. The proteins are electrophoresed in the above gels. The gels are then successively soaked in 50 mM HEPES, pH 7.6; 5 mM 2-mercaptoethanol and each of the following (for each wash): (a) 20% isopropanol; (b) no additions; (c) urea (6 M); (d) Urea (3 M); (e) Urea (0.75 M); and Tween 20 (0.05% vol:vol). Kinase reactions are then run by first soaking the gels in 20 mM HEPES, pH 7.6; 20 mM MgCl<sub>2</sub>; 2 mM DTT and then in the same buffer containing 0.02 M ATP (non-radioactive) with ca. 1000 cpm/pmol <sup>32</sup>P-γ-ATP. The gels are then washed six times with 5% trichloroacetic acid and 1% pyrophosphate. The gels are then stained with Coomassie brilliant blue dye (0.125%) in 50% methanol, 10% acetic acid; destained with 30% methanol, 10% acetic acid; soaked in 2% glycerol; and dried using a gel dryer. The gels are then exposed to autoradiography film for times ranging from several hours to weeks. The bands observed in the autoradiographs representing the gels reflect kinase activities. Mst 1 (apparent molecular weight about 59 kDa), Mst 2 (apparent molecular weight about 60 kDa), and a 34 kDa Mst kinase fragment are observed and identified by their migration as compared to the migration of molecular weight standards. The band intensities on the autoradiography film are quantitated by densitometry and comparisons between bands from untreated controls and bands from echistatin-treated cells provide the basis for the analyses.

## EXAMPLE 2

### Tablet composition

<u>Ingredient</u>	<u>Amount per tablet</u>
Simvastatin	10.0 mg
Geranylgeraniol	0.75 mg
BHA	0.02mg
Ascorbic acid	2.50 mg
Citric acid	1.25 mg

Microcrystalline cellulose	5.0 mg
Pregel starch	10.0 mg
Magnesium stearate	0.5 mg
Lactose	74.73 mg

- All the ingredients except magnesium stearate are blended together in a suitable mixer. The powder mixture is then granulated with adequate quantities of granulating solvent(s), e.g. water. The wet granulated mass is dried in a suitable dryer.
- 5 The dried granulation is sized through a suitable screen. The sized granulation is mixed with magnesium stearate before tableting. The tablets may be coated if deemed necessary. Additional ingredients that may be added to the above include suitable color and mixtures of colors.

- The composition is useful for treating or preventing elevated blood
- 10 cholesterol.

- In alternative formulations, the simvastatin is replaced by an HMG-CoA reductase inhibitor selected from lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or mevastatin, and the geranylgeraniol is replaced by geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl
- 15 propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, or geranylgeranyl glutarate

## EXAMPLE 3

Directly compressed tablet composition

<u>Amount per tablet</u>	<u>Ingredient</u>
10 mg	Lovastatin
0.75 mg	Geranylgeraniol
116.9 mg	Microcrystalline cellulose
116.9 mg	Lactose anhydrate
7.5 mg	Crosmellose sodium
3.7 mg	Magnesium stearate

5                   The ingredients are combined and blended together and are compressed using conventional tableting techniques.

                  The composition is useful for treating or preventing elevated blood cholesterol.

                  In alternative formulations, the simvastatin is replaced by an HMG-CoA  
 10    reductase inhibitor selected from lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or mevastatin, and the geranylgeraniol is replaced by geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, or geranylgeranyl glutarate

15

## EXAMPLE 4

Hard gelatin capsule composition

<u>Amount per capsule</u>	<u>Ingredient</u>
10 mg	Simvastatin
0.75 mg	Geranylgeraniol
47 mg	Microcrystalline cellulose
47 mg	Lactose anhydrate
1 mg	Magnesium stearate
1 capsule	Hard gelatin capsule

The dry ingredients are combined and blended together and encapsulated in a gelatin coating using standard manufacturing techniques.

The composition is useful for treating or preventing elevated blood cholesterol.

5 In alternative formulations, the simvastatin is replaced by an HMG-CoA reductase inhibitor selected from lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or mevastatin, and the geranylgeraniol is replaced by geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate,  
10 or geranylgeranyl glutarate

#### EXAMPLE 5

##### Oral suspension composition

<u>Amount per 5 mL dose</u>	<u>Ingredient</u>
10 mg	Lovastatin
0.75 mg	Geranylgeraniol
150 mg	Polyvinylpyrrolidone
2.5 mg	Poly oxyethylene sorbitan monolaurate
10 mg	Benzoic acid
to 5 mL with aqueous sorbitol solution (70%)	

15 An oral suspension is prepared by combining the ingredients using standard formulation techniques.

The composition is useful for treating or preventing elevated blood cholesterol.

20 In alternative formulations, the simvastatin is replaced by an HMG-CoA reductase inhibitor selected from lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or mevastatin, and the geranylgeraniol is replaced by geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate,  
25 or geranylgeranyl glutarate

## EXAMPLE 6

Intravenous infusion composition

<u>Amount per 200mL dose</u>	<u>Ingredient</u>
10 mg	Simvastatin
0.75 mg	Geranylgeraniol
0.2 mg	Polyethylene oxide 400
1.8 mg	Sodium chloride
to 200mL	Purified water

- 5                   The ingredients are combined using standard formulation techniques.  
The composition is useful for treating or preventing elevated blood cholesterol.

- 10                   In alternative formulations, the simvastatin is replaced by an HMG-CoA reductase inhibitor selected from lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or mevastatin, and the geranylgeraniol is replaced by geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, or geranylgeranyl glutarate

## WHAT IS CLAIMED IS:

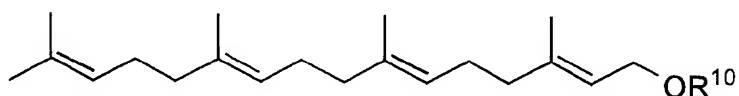
1. A pharmaceutical composition comprising an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

2. A composition according to claim 1 wherein said HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, mevastatin, and the pharmaceutically acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof.

3. A composition according to claim 2 wherein said HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and the pharmaceutically acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof.

4. A method according to claim 3 wherein said HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, and the pharmaceutically acceptable lactones, open acids, salts, and esters thereof, and mixtures thereof.

5. A composition according to any of Claims 1, 2, 3, or 4 wherein said geranylgeraniol compound corresponds to the chemical formula



wherein  $R^{10}$  is selected from the group consisting of H, C1-C30 alkyl, C2-C30 alkenyl, C2-C30 alkynyl, C5-C14 aryl,  $PO_3H_2$ ,  $P_2O_7H_3$ , and  $-C=O-R^{11}$ , wherein  $R^{11}$  is selected from the group consisting of H, C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C2-C10 hydroxy-substituted alkyl, C2-C10 amino-substituted alkyl, C2-C10 carbonylhydroxy-substituted alkyl, and C5-C14 aryl, and n is an integer from 0 to 3.

6. A pharmaceutical composition according to Claim 5 wherein  $R^{10}$  is selected from the group consisting of H,  $PO_3H_2$ ,  $P_2O_7H_3$ , and  $-C=O-R^{11}$ ,



wherein R<sup>11</sup> is selected from the group consisting of H, C1-C10 alkyl, C2-C10 hydroxy-substituted alkyl, C2-C10 amino-substituted alkyl, C2-C10 carbonylhydroxy-substituted alkyl, and C5-C14 aryl, and n is an integer from 2 to 3.

5                   7.       A pharmaceutical composition according to Claim 5 wherein R<sup>10</sup> is selected from the group consisting of H, PO<sub>3</sub>H<sub>2</sub>, P<sub>2</sub>O<sub>7</sub>H<sub>3</sub>, and -C=O-R<sup>11</sup>, wherein R<sup>11</sup> is selected from the group consisting of H, C1-C10 alkyl, C2-C10 hydroxy-substituted alkyl, C2-C10 amino-substituted alkyl, C2-C10 carbonylhydroxy-substituted alkyl, and C5-C14 aryl, and n is 3.

10                   8.       A pharmaceutical composition according to Claim 4 wherein said geranylgeraniol compound is selected from the group consisting of geranylgeraniol, geranylgeranyl ethyl ether, geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl  
15       benzoate, geranylgeranyl lactate, geranylgeranyl succinate, geranylgeranyl glutarate, and mixtures thereof.

                  9.       A pharmaceutical composition according to Claim 4 wherein said geranylgeraniol compound is selected from the group consisting of  
20       geranylgeraniol, geranylgeranyl phosphate, geranylgeranyl pyrophosphate, geranylgeranyl acetate, geranylgeranyl propionate, geranylgeranyl benzoate, geranylgeranyl lactate, geranylgeranyl succinate, geranylgeranyl glutarate, and mixtures thereof.

25                   10.       A pharmaceutical composition according to Claim 4 wherein said geranylgeraniol compound is selected from the group consisting of geranylgeraniol, geranylgeranyl pyrophosphate, and mixtures thereof.

30                   11.       A pharmaceutical composition which is prepared by combining an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

                  12.       A method for treating or preventing elevated blood cholesterol in a mammal in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

13. A method according to Claim 12 wherein said mammal is a human.

5 14. A method for treating or preventing arteriosclerosis in a mammal in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

10 15. A method according to Claim 14 wherein said mammal is a human.

15 16. A method for treating or preventing cardiovascular disease in a mammal in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

17. A method according to Claim 16 wherein said mammal is a human.

20 18. A method for treating or preventing a heart attack in a human in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

25 19. A method for treating or preventing stroke in a human in need thereof comprising administering an HMG-CoA reductase inhibitor and a geranylgeraniol compound.

20. A method for treating or preventing elevated blood cholesterol in a mammal in need thereof comprising sequentially administering a geranylgeraniol compound and an HMG-CoA reductase inhibitor.

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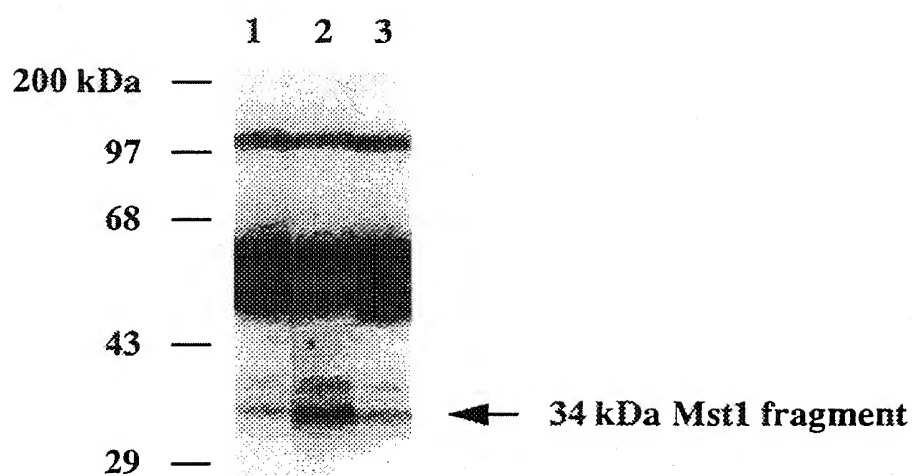


FIG. 1

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13887

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/405, 31/35, 31/21, 31/12

US CL :514/460, 510, 415, 689

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/460, 510, 415, 689

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,933,165 A (BROWN) 12 June 1990, see entire document.	1-20
A	US 5,316,765 A (FOLKERS et al) 31 May 1994, see entire document.	1-20
A	US 5,447,959 A (BORG) 05 September 1995, see entire document.	1-20
A	US 5,574,025 A (ANTHONY et al) 12 November 1996, see entire document.	1-20
A	US 5,639,653 A (BLOOM et al) 17 June 1997, see entire document.	1-20
A	US 5,763,646 A (KUMAR et al) 09 June 1998, see entire document.	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 SEPTEMBER 1999

Date of mailing of the international search report

**21 OCT 1999**

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